Severity of Head Injury Is Associated With Increased Risk of Coagulopathy in Combat Casualties

Andrew Peter Cap, MD, PhD; and Philip C. Spinella, MD, FCCM

Background: Traumatic brain injury (TBI) is believed to cause more profound trauma-induced coagulopathy than other injuries of comparable severity. This has not been reported in a large series of combat casualties in which penetrating injuries predominate.

Methods: Among US combat casualties severely injured in Iraq and Afghanistan who received transfused blood products, isolated TBI patients (head Abbreviated Injury Score [AIS] ≥ 3 and all other AIS < 2) were compared with non-TBI patients (head AIS ≤ 2 and any other AIS ≥ 3) to determine the degree to which TBI is associated with coagulopathy as measured by International Normalized Ratio (INR) and to describe characteristics of this population. Stepwise multiple regression analysis was also performed on all US casualties who received transfused blood products to analyze independent predictors of coagulopathy.

Results: We compared 117 patients with isolated TBI and 1,492 patients with non-TBI injuries. Admission INR was significantly higher in TBI patients. There were no differences in age, admission base deficit, systolic or diastolic blood pressure, or hemoglobin. On stepwise multiple regression, base deficit, Glasgow Coma Scale, and head AIS score were independently associated with increased coagulopathy as measured by INR.

Conclusion: Patients with severe combat-related trauma and isolated TBI had worse coagulopathy than non-TBI patients. Base deficit, Glasgow Coma Scale, and severity of head injury, as reflected by head AIS, are independently associated with increased coagulopathy as measured by INR.

Key Words: Traumatic brain injury, Coagulopathy, Combat, Trauma, Mortality.

(*J Trauma.* 2011;71: S78–S81)

The most common cause of mortality from traumatic injuries is severe head injury.[1] This is true for patients at both civilian trauma centers and for combat casualties.[2] Coagulopathy and shock secondary to injury increase the risk of death and disability for patients with severe traumatic brain injury (TBI).[3] Coagulopathy and shock are also associated with increased risk of massive transfusion and mortality in patients with severe systemic (non-TBI) injuries.[4,5]

Submitted for publication March 10, 2011.
Accepted for publication April 26, 2011.

From the US Army Institute of Surgical Research, Fort Sam Houston, Texas.
Supported by the US Army.
The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of the Army or Department of Defense.
The authors declare no conflict of interest.
Address for reprints: Andrew Peter Cap, MD, PhD, US Army Institute of Surgical Research, Building 3611, Fort Sam Houston, TX 78234; email: Andre.P.Cap@us.army.mil.

DOI: 10.1097/TA.0b013e3182218cd8

Coagulopathy is an abnormal state of coagulation, which can present as either a hypocoagulable state (prolonged clot formation and decreased clot strength because of dilution of factors) or a hypercoagulable state (rapid clot formation and increased clot strength).[6] Coagulation function is frequently measured as the International Normalized Ratio (INR), and coagulopathy has been defined as an INR ≥ 1.5.[7,8] Unfortunately, INR is insensitive to the complex molecular changes known and suspected to occur over time in trauma patients and may not accurately reflect important distinctions such as hypocoagulability or hypercoagulability.[7] It has been shown, however, that increased admission INR does predict morbidity, transfusion requirements, and mortality in trauma patients.[5] Resuscitation strategies intended to mitigate this acute coagulopathy of trauma have been recently described and are collectively known as "damage control resuscitation."[9,10] The fundamental concept underlying this approach is that the rapid recognition and prevention or treatment of coagulopathy and shock will decrease death from hemorrhage. Although this general concept has gained wide acceptance, it is important to determine whether the risk of coagulopathy is higher for certain patient populations, such as those with increased severity of head injury, because optimal coagulation function monitoring and therapy may differ for high-risk patients.

It is known that the effect of severe TBI on coagulation is complex, can lead to either a hypercoagulable or a hypocoagulable state, and can change over time.[3,11] Determining which factors are associated with an increased risk of coagulopathy is therefore important for tailoring therapy. Although previous reports have indicated that coagulopathy is common and is associated with increased morbidity and mortality for patients with severe TBI, it has not been determined whether the severity of TBI, as reflected by head Abbreviated Injury Score (AIS), is independently associated with the severity of coagulopathy.[12] In particular, this has not been examined in a large cohort that includes patients with severe non-TBI injuries. This relationship has also not been analyzed in patients with combat-related injuries. Our objective was to determine which factors, including measurements of the severity of head injury and indicators of shock, were associated with coagulopathy on admission among combat casualties.

MATERIALS AND METHODS

We performed a retrospective analysis of the Joint Theater Trauma Registry database of transfused casualties maintained at the US Army Institute of Surgical Research in

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 JUL 2011	**N/A**	**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Severity of head injury is associated with increased risk of coagulopathy in combat casualties	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
Cap A. P., Spinella P. C.,	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NUMBER
United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			
unclassified	**unclassified**	**unclassified**	**UU**	**4**	

San Antonio, TX. This database includes US military personnel injured and transfused with at least one blood product at combat support hospitals in either Iraq or Afghanistan. The quality of the data are maintained by examination of patient records and cross-referencing data for each patient within the database of blood products administered by the Armed Services Blood Program Office. US military personnel admitted to a combat support hospital with severe injuries and who received at least one blood product transfusion between October 2003 and January 2008 were analyzed. Severe injury was defined as AIS score of 3 or higher.

All epidemiologic, admission vital sign, and laboratory data between patients with isolated TBI (head AIS $\geq$3 and all other AIS $<$2) and non-TBI injuries (head AIS $\leq$2 and any other AIS $\geq$3) were compared to determine the degree to which TBI is associated with coagulopathy as measured by INR and to describe group characteristics of this population. Coagulopathy was defined as INR $\geq$1.5. The amount of blood products transfused, factor rVIIa administered, and outcomes between the two study groups were also compared. The following outcomes were compared: deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, stroke, acute respiratory distress syndrome, renal failure, mesenteric thrombosis, and 30-day mortality. Stepwise multiple regression analysis was performed to determine independent predictors of coagulopathy (INR was the continuous dependent variable). Independent variables analyzed within the regression model included admission temperature, systolic blood pressure (SBP), base deficit, hemoglobin, and AIS for all body regions. Severity of head injury was indicated by head AIS. Injury Severity Score (ISS) was not included in the model because it is a composite score derived from all AIS scores. Statistical analysis was performed with SPSS version 15.0 (SPSS Inc., Chicago, IL).

TABLE 1. Demographic, Admission, and Laboratory Variables of Non-TBI and Isolated TBI

Variable	Non-TBI (n = 1492), Median (IQR), Mean	Isolated TBI (n = 117), Median (IQR), Mean
Age (yr)	24 (21–28), 26	24 (21–27), 25
Pulse (beats/min)	108 (88–127), 109	80 (69–108), 89*
Respirations (breaths/min)	20 (16–24), 21	16 (14–20), 16*
Temperature (°F)	98.0 (97.2–99.0), 98.0	97.6 (96.0–98.9), 97.3†
SBP (mm Hg)	117 (97–134), 115	123 (95–142), 118
DBP (mm Hg)	64 (50–78), 65	66 (50–78), 66
GCS	15 (14–15), 13	3 (3–8), 6*
ISS	17 (10–24), 19	25 (17–26), 24*
Penetrating injury (%)	72.8	58.3*
BD (mmol/L)	5 (2–8), 6	4 (2–10), 7
Hemoglobin (g/dL)	12.0 (10.2–13.8), 11.8	12.0 (10.4–13.6), 11.8
INR	1.3 (1.1–1.6), 1.5	1.5 (1.3–2.1), 1.9*

* Mann-Whitney U Test or χ^2: $p \leq 0.001$.
† Mann-Whitney U Test or χ^2: $p < 0.05$.
IQR, inter-quartile range; BD, base deficit.

TABLE 2. Abbreviated Injury Severity Scores in Non-TBI and Isolated TBI

AIS Scores	Non-TBI (n = 1492), Median (IQR), Mean	Isolated TBI (n = 117), Median (IQR), Mean
Head	0.0 (0.0–0.0), 0.3	5.0 (4.0–5.0), 4.7*
Face	0.0 (0.0–0.0), 0.3	0.0 (0.0–0.0), 0.1†
Chest	0.0 (0.0–3.0), 1.1	0.0 (0.0–0.0), 0.0*
Abdomen	0.0 (0.0–2.0), 1.1	0.0 (0.0–0.0), 0.0*
Extremities	3.0 (3.0–3.0), 2.6	0.0 (0.0–0.0), 0.0*
External	1.0 (0.0–1.0), 1.0	0.0 (0.0–1.0), 0.5*

* All other comparisons: $p \leq 0.001$.
† Mann-Whitney U Test: $p = 0.011$.
IQR, inter-quartile range.

RESULTS

We analyzed a total of 1,609 transfused US military casualties with severe injury. The groups categorized into 117 patients with isolated severe TBI and 1,492 severe non-TBI patients. There was no difference between the isolated TBI group and the non-TBI group with respect to age, admission base deficit, SBP, diastolic blood pressure, and hemoglobin (Table 1). Pulse, respiratory rate, temperature, and Glasgow Coma Scale (GCS) did vary significantly between groups. Admission INR was significantly higher in isolated TBI patients (medians 1.3 vs. 1.5, $p < 0.001$). ISS was also significantly higher in isolated TBI patients (median 17 vs. 25, $p < 0.001$). AIS differed significantly between groups with head AIS (median score 5) driving ISS in isolated TBI patients and extremity AIS (median score 3) and external AIS (median score 1) driving ISS in non-TBI patients (Table 2). TBI patients were more likely to receive factor rVIIa than non-TBI patients (Table 3; 32 vs. 22%, $p = 0.006$). Patients without TBI received increased units of red blood cell (RBC), whole blood, and apheresis platelets, whereas plasma administration was similar between groups. This resulted in a higher plasma:RBC ratio in the TBI patient group and a higher platelet:RBC ratio in the non-TBI group (Table 3). The non-TBI group had an increased incidence of penetrating injuries (72.8 vs. 58.3%, $p < 0.001$; Table 1). There were no differences in the occurrence of DVT, PE, myocardial infarction, acute respiratory distress syndrome, renal failure, or mesenteric thrombosis between the groups (Table 4). TBI patients were 10 times more likely to develop stroke (2.6% 3 of 117 vs. 0.27% 4 of 1488, $p < 0.001$). Mortality was significantly higher in the TBI group (58.1 vs. 12.1%, $p < 0.001$; Table 4).

A stepwise multiple regression was conducted to investigate the best predictors of admission INR. A model that included the variables admission base deficit, GCS, and head AIS was statistically significant (F [3,695] = 92.11, $p < 0.001$). The regression coefficients (B) and the standardized regression coefficients (β) are listed in Table 5. The adjusted R^2 value was 0.281. This indicates that 28% of the variance in admission INR was explained by the model. Nonsignificant variables were admission temperature, SBP, hemoglobin, and AIS for other body regions.

DISCUSSION

The purpose of this analysis was to determine whether patients with an isolated TBI developed a more severe acute

TABLE 3. Use of Blood Components and Factor rVIIa in Non-TBI and Isolated TBI

Component (U)	Non-TBI (n = 1492), Median (IQR), Mean	Isolated TBI (n = 117), Median (IQR), Mean
RBC	6 (3–12), 10	4 (3–8), 6*
Plasma	3 (0–8), 6	3 (0–6), 4
Platelets	0.0 (0.0–0.0), 0.7	0.0 (0.0–0.0), 0.3†
Cryoprecipitate	0.0 (0.0–0.0), 0.3	0.0 (0.0–0.0), 0.3
Whole Blood	0.0 (0.0–0.0), 1.3	0.0 (0.0–0.0), 0.2*
SUM of RBCs	7 (4–15), 11	5 (3–8), 6*
Plasma:RBC	0.4 (0.0–0.8), 0.6	0.6 (0.0–1.0), 0.6†
Platelet:RBC	0.000 (0.000–0.000), 0.042	0.000 (0.000–0.000), 0.039†
Factor rVIIa use (%)	22.2	33.3‡

Mann-Whitney *U* Test or χ^2: $p \leq 0.001$.
† Mann-Whitney *U* Test or χ^2: $p < 0.05$.
‡ Mann-Whitney *U* Test or χ^2: $p = 0.006$.
SUM of RBCs represents total packed RBC plus whole blood units. Platelet units were exclusively apheresis units.
IQR, inter-quartile range.

TABLE 4. Complication and Mortality Rates in Non-TBI and Isolated TBI

Outcome	Non-TBI (n = 1492), %	Isolated TBI (n = 117), %
Deep venous thrombosis	7.4	3.4
Pulmonary embolism	1.7	5.5
Myocardial infarction	0.5	1.7
Stroke	0.3	2.6*
Acute respiratory distress syndrome	5.4	3.4
Renal failure	4.4	0.0
Mesenteric thrombosis	0.0	0.0
Death	12.1	58.1*

* χ^2: $p \leq 0.001$.

TABLE 5. Stepwise Multiple Regression Analysis for Variables Predicting Admission INR

Variable	B	Standard Error B	β
Admission base deficit	0.065	0.005	0.450*
GCS	−0.024	0.007	−0.136*
Head AIS	0.046	0.021	0.078†
Constant	1.361	0.109	

$R^2 = 0.284$; F (3, 695) = 92.11, $p < 0.001$.
* $p \leq 0.001$.
† $p = 0.025$.

coagulopathy of trauma than severely combat-injured patients without significant head injury. The importance of determining whether TBI has a differential effect on coagulopathy is that it might affect the threshold for coagulation monitoring and alter therapy aimed at treating coagulopathy in these patients.

The current analysis is unique in that it documented an increased severity of coagulopathy in patients with isolated head injury compared with that observed in severely injured combat casualties without head injury. All 1,609 patients in this analysis were injured severely enough to require blood product transfusions. Through multiple regression analysis in this combined patient cohort, an independent association between severity of head injury and acute traumatic coagulopathy, as measured by admission INR, was identified.

A recent review focusing on patients with severe TBI indicates that there is an independent association between coagulopathy and mortality.[3] Harhangi et al. performed a meta-analysis of 34 studies and reported an overall prevalence of coagulopathy of 32.7% in TBI patients. The main result of this meta-analysis was that the presence of coagulopathy after TBI was independently associated with increased mortality (odds ratio 9.0; 95% confidence interval 7.3–11.6) and unfavorable outcome (odds ratio 36.3; 95% confidence interval 18.7–70.5).

The current results indicate that severity of head injury and measures of shock were both independently associated with an increased risk of acute coagulopathy of trauma in a severely combat-injured patient population. These results are consistent with those recently reported in civilian trauma population.[13] The significance of these results is that those presenting with increased severity of head injury and shock may benefit from increased coagulation monitoring and potentially may require alternative resuscitation and coagulation management strategies compared with those with only systemic injuries. These results indicate that TBI patients did indeed undergo resuscitations that differed significantly in blood product and factor rVIIa use from those received by non-TBI patients. It is not known whether differences in resuscitation were beneficial or harmful, particularly because the use of rVIIa has not been prospectively validated in managing TBI.[14,15] This is also due, in part, to the fact that currently, the coagulation monitoring data available from combat hospitals are limited to INR values. These are inadequate to describe the dynamic changes in coagulation system function likely to be occurring in patients with severe TBI. Furthermore, it is unknown whether the complex molecular changes reflected in relatively insensitive INR values are similar between TBI and non-TBI patients.

The ability to determine clot formation kinetics, overall clot strength, and kinetics of fibrinolysis for patients with severe TBI and shock would be useful in differentiating hypercoagulability from early disseminated intravascular coagulation. The implementation of goal-directed coagulation therapy might be possible if such parameters were measured accurately and in near real time.[16–19] It might also be possible to differentiate the coagulopathy that occurs in TBI versus non-TBI patients and tailor therapy accordingly. Viscoelastic coagulation monitoring methods such as thromboelastography or rotational thromboelastometry offer these capabilities, but resuscitation strategies based on their output have not yet been prospectively validated. Furthermore, these methods may be difficult to implement as results may vary significantly with operator experience and institutional protocol.[20]

The limitations of this study reflect the difficulties of studying combat casualties, namely the near impossibility of

performing prospective, randomized studies, and our consequent reliance on retrospective analyses. Only patients who survived long enough to receive blood product transfusions were studied. It is possible that factors other than those identified in this study are better predictors of coagulopathy as measured by admission INR, particularly in those patients experiencing early mortality. Adverse event reporting for complications such as DVT and PE was performed on an ad hoc basis and was based on clinical impression and available laboratory and radiographic studies rather than on predefined screening algorithms and diagnostic criteria. It is possible that complications were underdiagnosed or misdiagnosed. The categorization of patients into isolated TBI and non-TBI cohorts was fundamental to the study objectives but had the effect of creating groups unbalanced with respect to important prognostic variables such as ISS and GCS. It is possible that clinical or laboratory variables that correlate with ISS and GCS but that were not considered in this analysis may have greater power in predicting severity of coagulopathy. Finally, these observations show only an association between shock, severity of head injury, and severity of coagulopathy and do not demonstrate causation or define mechanisms. As such, these observations are hypothesis generating and should not be used to define patient-care guidelines.

CONCLUSIONS

Patients with severe combat-related trauma and isolated TBI had more severe acute coagulopathy of trauma than non-TBI patients. Base deficit, GCS, and severity of head injury, as reflected by head AIS, are independently associated with coagulopathy as measured by admission INR.

REFERENCES

1. Dewall J. The ABCs of TBI. Evidence-based guidelines for adult traumatic brain injury care. *JEMS.* 2010;35:54–61; quiz 63.
2. Kelly JF, Ritenour AE, McLaughlin DF, et al. Injury severity and causes of death from Operation Iraqi Freedom and Operation Enduring Freedom: 2003–2004 versus 2006. *J Trauma.* 2008;64(suppl 2):S21–S26; discussion S26–S27.
3. Harhangi BS, Kompanje EJ, Leebeek FW, Maas AI. Coagulation disorders after traumatic brain injury. *Acta Neurochir (Wien).* 2008;150: 165–175; discussion 175.
4. Niles SE, McLaughlin DF, Perkins JG, et al. Increased mortality associated with the early coagulopathy of trauma in combat casualties. *J Trauma.* 2008;64:1459–1463; discussion 1463–1455.
5. Brohi K, Cohen MJ, Ganter MT, Matthay MA, Mackersie RC, Pittet JF. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? *Ann Surg.* 2007;245:812–818.
6. Park MS, Martini WZ, Dubick MA, et al. Thromboelastography as a better indicator of hypercoagulable state after injury than prothrombin time or activated partial thromboplastin time. *J Trauma.* 2009;67:266–275; discussion 275–276.
7. Dunbar NM, Chandler WL. Thrombin generation in trauma patients. *Transfusion.* 2009;49:2652–2660.
8. Jeger V, Urwyler N, Zimmermann H, Exadaktylos AK. Trauma-induced coagulopathy in severely injured patients: knowledge lost in translation? *Emerg Med J.* 2010;27:551–552.
9. Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma.* 2007; 62:307–310.
10. Spinella PC, Holcomb JB. Resuscitation and transfusion principles for traumatic hemorrhagic shock. *Blood Rev.* 2009;23:231–240.
11. Lustenberger T, Talving P, Kobayashi L, et al. Time course of coagulopathy in isolated severe traumatic brain injury. *Injury.* May 12, 2010. ePub ahead of print.
12. Talving P, Benfield R, Hadjizacharia P, Inaba K, Chan LS, Demetriades D. Coagulopathy in severe traumatic brain injury: a prospective study. *J Trauma.* 2009;66:55–61; discussion 61–62.
13. Lustenberger T, Talving P, Kobayashi L, et al. Early coagulopathy after isolated severe traumatic brain injury: relationship with hypoperfusion challenged. *J Trauma.* 2010;69:1410–1414.
14. Perel P, Roberts I, Shakur H, Thinkhamrop B, Phuenpathom N, Yutthakasemsunt S. Haemostatic drugs for traumatic brain injury. *Cochrane Database Syst Rev.* 2010:CD007877.
15. Hauser CJ, Boffard K, Dutton R, et al. Results of the CONTROL trial: efficacy and safety of recombinant activated Factor VII in the management of refractory traumatic hemorrhage. *J Trauma.* 2010; 69:489–500.
16. Johansson PI. Goal-directed hemostatic resuscitation for massively bleeding patients: the Copenhagen concept. *Transfus Apher Sci.* 2010; 43:401–405.
17. Schöchl H, Nienaber U, Hofer G, et al. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. *Crit Care.* 2010;14:R55.
18. Schöchl H, Forster L, Woidke R, Solomon C, Voelckel W. Use of rotation thromboelastometry (ROTEM) to achieve successful treatment of polytrauma with fibrinogen concentrate and prothrombin complex concentrate. *Anaesthesia.* 2010;65:199–203.
19. Nylund CM, Borgman MA, Holcomb JB, Jenkins D, Spinella PC. Thromboelastography to direct the administration of recombinant activated factor VII in a child with traumatic injury requiring massive transfusion. *Pediatr Crit Care Med.* 2009;10:e22–e26.
20. Kitchen DP, Kitchen S, Jennings I, Woods T, Walker I. Quality assurance and quality control of thrombelastography and rotational thromboelastometry: the UK NEQAS for blood coagulation experience. *Semin Thromb Hemost.* 2010;36:757–763.